REMARKS

The Office Action dated June 9, 2004 dated presents the examination of claims 1-18. Claims 19 and 20 are withdrawn from consideration. Claims 2-3, 5-16, and 18 are amended. These amendments are non-narrowing claim amendments made to clarify claim language. Claims 19 and 20 are canceled. Claims 21 and 22 are added. Support for claims 21 and 22 is found in original claims 9 and 17, respectively. No new matter is inserted into the application.

Election/Restriction

The Examiner maintains the Restriction Requirement such that claims 19 and 20 are withdrawn from consideration. Claims 19 and 20 are canceled, thus rendering the Restriction Requirement moot.

Claim Objections

The Examiner objects to claims 9 and 11-17 under 37 C.F.R. § 1.75(c) for allegedly being in improper multiple dependent form. Applicants respectfully submit that the pending claims, as amended, do not recite improper multiple dependencies. Thus, the instant objection is overcome.

The Examiner also objects to claims 5-7 and 10 for minor grammatical informalities. Applicants respectfully traverse.

Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

In order to overcome the objection, the phrase "at between" in claim 5 is amended to "between" and the phrase "different sequences in each other" in claims 6, 7, and 10 is amended to "wherein the mutant FRT sequences are different relative to one another in the 8-bp spacer region." Withdrawal of the instant objection is therefore respectfully requested.

Rejection under 35 U.S.C. § 101

The Examiner rejects claims 1-7 and 18 under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that claims 1-7 do not sufficiently distinguish the claimed DNA from nucleic acids as they exist naturally, because "the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products." See, page 3, lines 20-21 of the Office Action.

Applicants respectfully disagree. Claim 1 is directed to a DNA comprising a mutant FRT sequence shown in any one of SEQ ID NOS: 2-5. These mutant FRT sequences are not found in nature. In other words, the DNA of claim 1 is an artificial DNA made by man. As

pronounced by the Supreme Court in Diamond v. Chakrabarty, patentable subject matter under 35 U.S.C. § 101 includes "anything under the sun that is made by man." 447 U.S. 303, 308-09 (1980). Therefore, the DNA of claim 1 is patentable subject matter under 35 U.S.C. § 101 since it is an artificial DNA.

The Examiner asserts that claim 18 encompasses a transgenic human. Claim 18 is amended to recite a transgenic non-human animal. Thus, the instant rejection is overcome.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 8 and 10 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter not enabled by the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the specification, while being enabling for the method for replacing a gene of claim 10 *in vitro*, does not reasonably provide enablement for the method for replacing a gene of claim 10 *in vivo*. The Examiner also asserts that the specification fails to provide enablement for a cell *in vivo*. Applicants respectfully disagree.

The present invention, as recited in claim 10, is directed to a method for replacing a nucleotide sequence. As noted by the Examiner, the method of claim 10 encompasses both an *in vitro* and

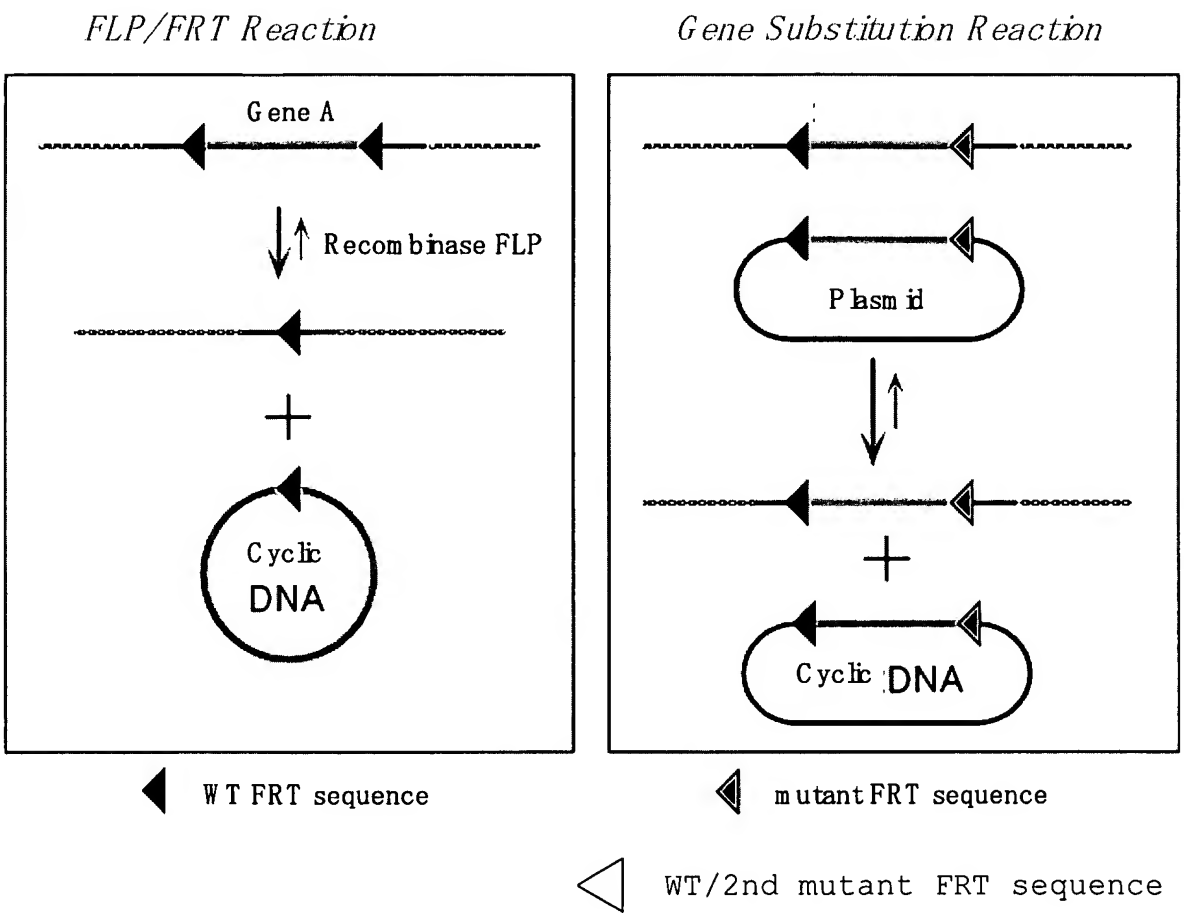
an *in vivo* reaction. However, the Examiner spends the majority of the Office Action discussing the state of the art of gene therapy, including the predictability thereof. While Applicants agree that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention, the scope of enablement must only bear a "reasonable correlation" with the scope of the claims. In re Fisher, 427 F.2d 833, 839 (CCPA 1970).

Since the claim 10 is directed to a method for replacing a nucleotide sequence, rather than a method for gene therapy *per se*, the Examiner errs by focusing his rejection on the predictability of the latter. Gene substitutions reactions are known in the art and readily practiced by the skilled artisan both *in vitro* and *in vivo* without undue experimentation. Therefore, contrary to the Examiner's remarks, the full scope of claim 10 is enabled by the specification.

The gene substitution reaction is shown in the right panel of Figure 1 (below). As shown therein, a target gene can be replaced with another gene of interest located on a plasmid in between a wild-type FRT sequence and the mutant FRT sequence of the present invention, in the presence of recombinase FLP. See also, pages 1 to 3 and Example 4 of the specification. The FLP/FRT reaction is shown in the left panel of Figure 1. Unlike the nucleotide sequence substitution reaction of the present invention, a target

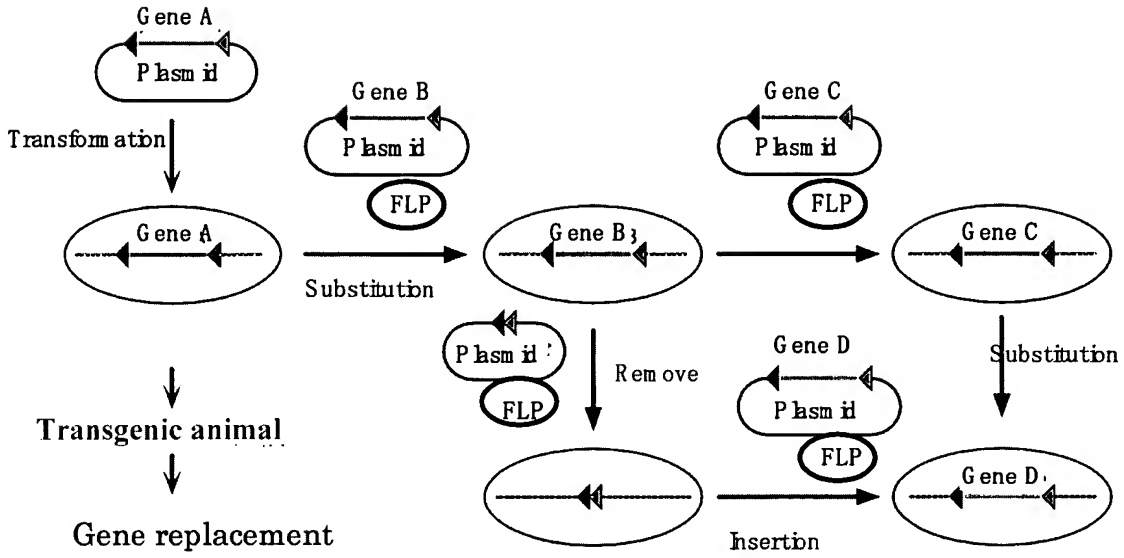
gene ("Gene A") located in between two wild-type FRT sequences will only be deleted.

Figure 1



Therefore, when a transgenic animal carries the mutant FRT sequence of the present invention, a desired nucleotide sequence can be introduced into the transgenic animal using the nucleotide sequence substitution reaction. See Figure 2 (below).

Figure 2



Prior to the priority date of the present application, it was well known in the art that recombination in a transgenic mouse could be achieved through the use of the recombinase Cre-LoxP sequence system. As evidence thereto, references 1 to 6 are attached.

In the recombinase Cre-LoxP sequence system, *in vivo* recombination of a target gene takes place in a progeny of a LoxP-transgenic mouse mated with a *cre*-transgenic mouse (see references 1 to 3), or in a mouse in which the Cre-expressing viral vector has been administered (see reference 4 to 6).

Reference 1 (*Proc. Natl. Acad. Sci.*, USA, 89, 6232-6236 (1992)) discloses that a mouse expressing TAg (tumor antigen) is obtained when a *cre*-transgenic mouse is mated with a loxP-His3pA-loxP-TAg-transgenic mouse. See e.g., Abstract, Fig. 1, etc.

Reference 2 (*Proc. Natl. Acad. Sci., USA*, 89, 6861-6865 (1992)) discloses that when a LoxP-β-Gal-LoxP- transgenic mouse is mated with *cre*-transgenic mouse, a mouse is generated in which β-Galactosidase is knocked out of the Cre-expressing cells. See e.g., Abstract, Fig. 1, etc. Reference 3 (*Science*, 269, 1427-1429 (1995)) discloses that when a LoxP-DNA polymerase β-LoxP-transgenic mouse is mated with a *cre*-transgenic mouse, a mouse is generated in which the DNA polymerase β gene is removed in Cre-expressing hepatocytes or lymphocytes. See e.g., Abstract, Fig. 1.

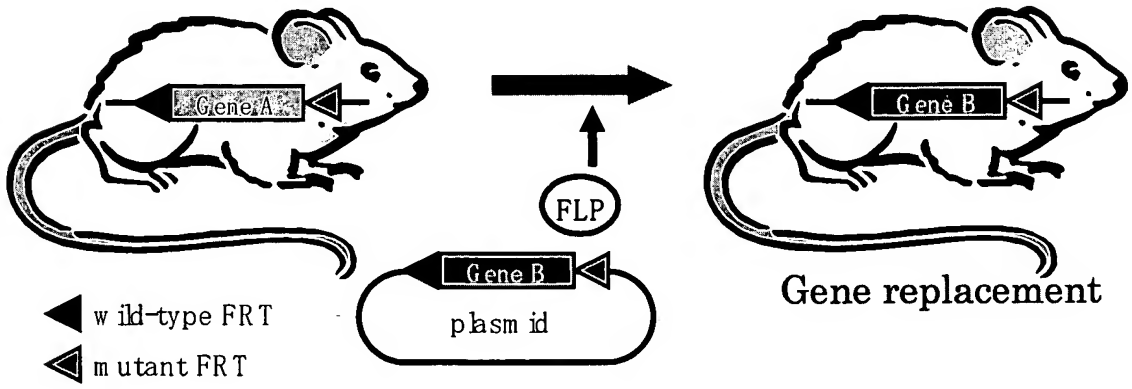
Reference 4 (*Nucleic Acids Research*, 25, 1766-1773 (1997)) discloses in that when a LoxP-CAT-pA-LoxP -lacZ -transgenic mouse is administered an adenovirus vector carrying the Cre expression system (Cre adenovirus vector), the resulting mouse expresses lacZ due to the deletion of the CAT gene in the Cre expressing cells. See e.g., Abstract, Fig. 1. Reference 5 (*Proc. Natl. Acad. Sci., USA*, 93, 3932-3936 (1996)) discloses that a mouse expressing Tag is obtained by administering a Cre adenovirus vector to a LoxP-Stop sequence-LoxP -Tag -transgenic mouse, thereby allowing for the deletion of the stop sequence in Cre expressing cells. See e.g., Abstract, Fig. 1. Reference 6 (*The Journal of Biological Chemistry*, 273, 9001-9006 (1998)) discloses a mouse, in which a HCV derived gene is expressed, obtained by administering a Cre adenovirus vector to a LoxP-neo-pA-LoxP -HCV cDNA-pA -transgenic

mouse, thereby allowing for the deletion of neo in the Cre expressing hepatocytes. See e.g., Abstract, Fig 1.

Therefore, one of ordinary skill in the art understands that when recombination can be carried out *in vitro*, the recombination can be carried out *in vivo* in the same manner.

As shown below in Figure 3 (below), when a plasmid carrying "Gene B", which flanked by the mutant FRT sequence of the present invention and the wild-type FRT sequence is administered (such as via a vein, muscle, the brain or the like, or subcutaneously) to an animal carrying "Gene A", flanked by the mutant FRT sequence of the present invention and the wild-type FRT sequence, "Gene A" in the animal is replaced with "Gene B" of the plasmid in the presence of recombinase FLP. Thus, contrary to the Examiner remarks, nucleotide sequence replacement using the mutant FRT sequence of the present invention is enabled by the present specification.

Figure 3



For all of the above reasons, Applicants respectfully submit that the instant claims are fully enabled by the specification. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 2, 3, 6, 7, and 10 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that the phrase "the mutant FRT sequence consists of a sequence further comprising substitutions of at least one nucleotide in a region other than the spacer region in the mutant FRT sequence defined in claim 1" is indefinite. Claim 2 is amended to recite that the DNA comprises at least one nucleotide substitution in the mutant FRT sequence other than in the 8-bp spacer region spanning nucleotide positions 14-21. Thus, the instant rejection is overcome.

The Examiner also asserts that the phrase "two mutant FRT sequence having different sequences in each other defined in claim 3" recited in claims 6 and 7 is indefinite. Claim 6 is amended to recite a DNA comprising at least two mutant FRT sequences defined in claim 3, wherein the mutant FRT sequences are different relative

to one another in the 8-bp spacer region. Thus, the instant rejection is overcome.

Applicants respectfully submit that the pending claims particularly point out and distinctly claim the subject matter of the present invention. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 102

The Examiner rejects claims 2, 3, 6, 7, and 10 under 35 U.S.C. § 102(b) for allegedly being anticipated by Schlake et al. (*Biochemistry*, 33, 12746-12751, 1994) or Siebler et al. (*Nucleic Acids Research*, 36, 1740-1747, 1997).

Schlake et al. and Siebler et al. disclose several mutant FRT sequences. As acknowledged by the Examiner, neither Schlake et al. nor Siebler et al. disclose a DNA comprising a mutant FRT sequence shown in any one of SEQ ID NOS: 2-5.

Claim 2, as amended, is directed to a DNA comprising a mutant FRT sequence shown in any of SEQ ID NOS: 2-5, wherein the mutant FRT sequence further comprises at least one nucleotide substitution other than in nucleotide positions 14-21 (i.e., the spacer region). Since none of the sequences disclosed in Schlake et al. or Siebler et al. comprise any of SEQ ID NOS: 2-5, these references also fail to disclose the subject matter of claims 2, 3, 6, 7, and 10.

For this reason, Schlake et al. and Siebler et al. fail to anticipate the present invention. Withdrawal of the instant rejection is therefore respectfully requested.

Conclusion

Applicants respectfully submit that the above remarks and/or amendments fully address and overcome the outstanding rejections and objections. For the foregoing reasons, Applicants respectfully request the Examiner to withdraw all of the outstanding rejections and objections, and to issue a Notice of Allowance indicating the patentability of the present claims. Early and favorable action of the merits of the present application is thereby respectfully requested.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of three (3) months to December 9, 2004, in which to file a reply to the Office Action. The required fee of $980.00 is enclosed herewith.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments:

Lakso et al.; Proc. Natl. Acad. Sci. Vol. 89; pp. 6232-6236; July 1992;

Orban et al.; Proc. Natl. Acad. Sci. Vol. 89; pp. 6861-6865; August 1992;

Kühn et al.; Science; Vol. 269; pp. 1427-1429; Sept. 8, 1995;

Akagi et al.; Nucleic Acids Research; Vol. 25; No. 9; pp. 1766-1773; 1997;

Wang et al.; Proc. Natl. Acad. Sci. Vol. 93; pp. 3932-3936; April 1996;

Wakita et al.; The Journal of Biological Chemistry; Vol. 273; No. 15; pp. 9001-9006; April 10, 1998